RESPONSE

I. Status of the Claims

Claims 1 and 2 have been amended and new Claims 5-8 have been added. Claims 1-8 are therefore presently pending in the case. In an attempt to comply with 37 C.F.R. §1.121 and for the convenience of the Examiner a clean copy of the pending claims is attached hereto as **Exhibit A.**

II. Support for the Amended Specification and Claims

Claim 1 has been amended in response to an objection and to further clarify the claim. Amendment of Claim 1 finds support throughout the specification as originally filed with particular support being provided by the original Claim 1.

Claim 2 has been amended to further clarify the claim, and to recite highly stringent conditions. Amendment of Claim 2 finds support throughout the specification as originally filed with particular support and a definition of highly stringent hybridization being found in the specification at page 5, lines 11-18.

Claim 5 has been added to more clearly claim certain aspects of the invention. Claim 5 finds support throughout the specification as originally filed, with particular support being found at least at page 15, lines 1-8.

Claim 6 has been added to more clearly claim certain aspects of the invention. Claim 6 finds support throughout the specification as originally filed, with particular support being found at least at page 15, lines 1-8.

Claim 7 has been added to more clearly claim certain aspects of the invention. Claim 7 finds support throughout the specification as originally filed, with particular support being found at least at page 15, lines 8-14.

Claim 8 has been added to more clearly claim certain aspects of the invention. Claim 8 finds support throughout the specification as originally filed, with particular support being found at least at page 15, lines 8-14.

As the amendment to Claims 1 and 2 and new claims 5-8 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is

respectfully requested.

III. Objection

Objections within the specification and in Claim 1 have been addressed by the submitted amendments.

IV. Rejection of Claims 1-4 Under 35 U.S.C. § 101

The Action first rejects claims 1-4 under 35 U.S.C. § 101 because the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well-established utility. Applicants respectfully disagree.

The Action gives a number of reasons for the alleged lack of utility. First, the Action states that "The specification does not disclose any data for any activity for the polypeptides encoded by SEQ ID NO:1. There are no working examples" (Action at page 3, last lines of section 6). Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986) and it is well established that "an inventor is not required to understand the theory of how his invention works". *Micro Motion, Inc. v. Exac Corp.*, 16 USPQ2d 1001, 1013 (Cal. 1990). The statement that "There are no working examples" is also misplaced, for it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962).

The Action (pages 3-4) appears to recognize Applicants' assertion that the sequences of the present invention encode sodium-calcium exchanger protein variants and that "Applicants assertion that SEQ ID NO:1 encodes an ion exchanger is credible" (Action at page 4, lines 2-3). However, it does not recognize that the sequences of the present invention have a specific or substantial utility as "the art recognizes a large number of Na^+/Ca^+ counter transporters" (Action page , lines 4-5). In support of this position the Action cites Linck *et al.* (American Journal of Physiology, **274**:C415-423, 1998) as teaching that there are three isoforms of a mammalian Na^+/Ca^+exchangers (NCX1, NCX2, NCX3) which differ in their expression patterns and that "It is not clear from the specification...what tissues are it expressed in" (Action at page 4, lines 11-13). Applicants respectfully disagree and invite the

Examiners attention to the first paragraph of Section 5 of the specification in which it is said that the sequences of the present invention are "expressed in, *inter alia,* human cell lines, fetal brain, brain, pituitary, cerebellum, spinal cord, lymph node, lung, prostate, adrenal gland, skeletal muscle, esophagus, pericardium, hypothalamus, fetal kidney, tongue, 6-12 (*sic*) week embryos, and osteosarcoma cells". Thus clearly the specification describes what tissues express the sequences of the current invention.

The Action then goes on to make the point that Applicants assertion is not substantial because the art acknowledges that function cannot be predicated from structure. In support of this position the Action then cites several articles.

First, the Action cites an article by Skolnick and Fetrow ("Skolnick"; 2000, TIBTECH **18**:34-39) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used, as described by Ji, to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus arguing against the conclusion drawn in the Action.

The Action next cites Bork (Genome Research **10**:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1, on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have

employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement.

The Action next cites Doerks *et al.* (Trends in Genetics **14**:248-250, 1998) in support that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Applicants point out that transporters represent a well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Action's position against utility, Doerks *et al.* supports Applicants' position that the presently claimed sequences have a recognized substantial and credible utility.

The Action also cites Smith and Zhang (Nature Biotechnology ***15***:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous" (Action at page 3). First it should be noted that the Smith and Zhang article precedes the filing date of the provisional U.S. patent application no. 60/210,271, filed on June, 8 2000, to which the present application claims benefit by three years and may therefore no longer represents the state of the art three years later. Aside from that fact, the Smith and Zhang article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first

paragraph, emphasis added). Thus, Smith and Zhang do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

Additionally, the Action cites Brenner (TIG ***15***:132-133, 1999) as teaching that "most homologs must have different molecular and cellular functions" (Action at page 3). However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants. Thus, the Brenner article also does not support the alleged lack of utility.

The Action also cites Bork *et al.* (Trends in Genetics ***12***:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 6 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination-the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure-function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). Clearly such highly skilled and

careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes cleat that Bork *et al.* do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Applicants assertions regarding the utility of the present invention.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 2 Ph.D. level scientists). These articles are merely examples of a small number of spurious publications that call into doubt the usefulness of bioinformatic predictions and that the PTO has repeatedly attempted to use as a basis to deny the utility of nucleic acid sequences. However, without going into the merits (or lack thereof) of all of the cited articles, Applicants point out that the lack of 100% unanimous agreement on the usefulness of bioinformatic prediction programs or the derivation of function using established domains and motifs is completely irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Applicants submit that the overwhelming majority of those of skill in the relevant art **believe** bioinformatic prediction to be a powerful and useful tool, and that the derivation of function using established protein domains and shared motifs is often essential to defining function, this is evidenced by hundreds if not thousands of published journal articles.

Rather, the question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing

some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between

35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Applicants' assertion that the sequences of the present invention encode variants of Na+/Ca+ exchanger proteins, more specifically splice variants of NCX4 (SLC8A3), is supported by the evidence provided in **Exhibit B**, which contains an amino acid sequence comparison between SEQ ID NO:2 and an amino acid sequence that is identical to SEQ ID NO:2 of the present invention that is present in the leading scientific repository for biological sequence data (GENBANK). This sequence, GENBANK Accession No. AF510501 (information provided as **Exhibit C**) has been annotated by third party scientists *wholly unaffiliated with Applicants* as "Homo sapiens Na+/Ca+ exchanger isoform 3 splice varient 2 (SLC8A3) (GenBank accession number AF510501) which is described in a publication entitled "The human SLC8A3 gene and tissue-specific Na+/Ca2+ exchanger 3 isoforms" by Gabellini, *et al.* (Gene, **298**:1-7, 2002: Abstract provided as **Exhibit D**). This publication constitutes evidence that clearly demonstrates that the exchanger proteins of the present invention have

function and utility that are both accepted by those skilled in the art. As the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. In the present instance, the Examiner has argued that in spite of shared structural features that those skilled in the art would not believe that a protein has a given biochemical activity. Clearly those of skill in the art would recognize that molecules that share identical amino acid sequences would share protein structure and would thus also have the same function. Given this clear evidence that those skilled in the art have independently assigned Na+/Ca+ exchanger function and activity there can be no question that Applicants' asserted utility for the described sequences is "credible" and constitutes a post filing date publication that clearly supports the specifications assertion that SEQ ID NO:1 has the function of a known Na+/Ca+ exchanger protein.

Applicants submit that the presently claimed molecules have been shown to encode, as asserted in the specification as filed, Na+/Ca+ exchanger poroteins, whose biological function is known to the art. Thus, the present situation directly tracks Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the 100 % identity between the presently claimed sequences and those of the cited Na+/Ca+ exchanger isoform (SLC8A3). In particular the present invention has a number of additional substantial and credible utilities, not the least of which relates to polymorphisms identified in the sequences of the present invention described in the specification in the second paragraph of Section 5.1 on page 17. Two polymorphisms were identified during the sequencing of the NHIEPs including an A/G polymorphism at the nucleotide position represented by, for example, position 1889 of SEQ ID NO:1 (which can result in an asp or gly at corresponding amino acid (aa) position 630 of, for example, SEQ ID NO:2), and either the presence or absence of an extra GCA triplet at nucleotide position 2113 (which can result in the addition of an extra ala at aa position 705 of, for example, SEQ ID NO:2).

These polymorphisms provide significant and specific utility as taught in the specification. Such polymorphisms have significant and specific utility in, *intra alia*, the fields of forensic science, human

population biology and in the resolution of paternity issues. Such polymorphisms can also be used as specific markers useful, for example, in identifying human remains, determining human group migration patterns by identifying descendants of a specific group and in addition clearly the polymorphism of the present invention has significant and specific utility in resolving issues of paternity. The utility and use of such nucleic acid polymorphisms in forensic science, for example, to identify a deceased individual or to link an individual to a crime can result in incarceration or execution of a human being. Clearly the incarceration or execution of a human being is highly significant and thus the utility of nucleic acid polymorphisms in forensic science is substantial. Similarly, the use of such nucleic acid polymorphisms in identification of paternity results in both significant emotional and financial burdens, and thus the utility of nucleic acid polymorphisms in paternal analysis is also substantial. Further, Applicants submit that these utilities are not only credible, but well established and known to those of skill in the art. As such polymorphisms are the basis for forensic analysis, paternity identification and population biology studies, which are undoubtedly "real world" utilities, the present sequences must in themselves be useful. It is important to note that the presence of more useful polymorphic markers for such analysis would not mean that the present sequences lack utility.

Applicants submit that the presently described polymorphism is useful in forensic analysis **exactly as it was described in the specification as originally filed**. Individual members of a population can be distinguished based on the presence or absence of the described polymorphism, and thus, these sequences are useful without "additional research". Simply because the use of this polymorphic marker will necessarily provide additional information on the percentage of particular subpopulations that contain this polymorphic marker does not mean that "additional research" is needed in order for this marker as it is presently described in the instant specification to be of use to forensic science. Thus, the Examiner's position does not support the alleged lack of utility.

This is also not a case of a potential utility. As stated above, using the presently described polymorphic marker as described in the specification as originally field will definitely distinguish members of a population from one another. In the worst case scenario, this marker is useful to distinguish 50% of the population (in other words, the marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis **clearly** is a real world, practical utility. Applicants fail to understand how, given the widespread and daily use of forensic analysis to

distinguish individuals, the use of a polymorphic marker in forensic analysis is not a "substantial" use. With regard to the allegation that the use of the presently described polymorphism in forensic analysis is not a "specific" use, as set forth in the Response to the Final Action, Applicants submit that this is improper on a number of different grounds. First, and most importantly, the Final Action seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that other polymorphic markers have been identified in other genetic loci does not mean that Applicants' identification of a polymorphic marker in SEQ ID NO:1 is not specific. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because other polymorphic sequences from the human genome have been described does not mean that the use of the presently described polymorphic markers for forensic analysis is not a specific utility. The requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an improper standard. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, just to name a few particular examples, because examples of each of these have already been described and patented. However, only the briefest perusal of any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, Applicants submit that the asserted forensic utility is specific because it cannot be applied to just any nucleic acid. In fact, the basis for forensic analysis is the fact that such a polymorphic marker is **not** present in all other nucleic acids, but in fact specific and unique to only a

certain subset of the population. As such, the presently described polymorphic marker clearly has a specific utility, and therefore the presently claimed invention must meet the requirements for utility under 35 U.S.C. § 101.

Still further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions as described in the specification. The Action notes (page 9, section f), but disputes, Applicants' assertion that the sequences of the present invention have utility in the identification of coding sequence and mapping a unique gene to a particular chromosome as well as the identification of actual biologically relevant exon splice junctions. The Action states that substantial further research would be required for the skilled artisan to determine where this particular sequence is mapped. Applicants strongly disagree and provide the following evidence. Provided as evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided as **Exhibit E**. This is the result of overlaying the sequence of SEQ ID NO: 1 of the present invention and the identified human genomic sequence. By doing this one is able to identify the portions of the genome that encode the present invention. If these regions of the genome are non-contiguous, this is indicative of individual exons. The results of such an analysis indicates that the sequence of the present invention is encoded by more than 6 exons spread non-contiguously along a region of human chromosome 14, (as stated in the specification as filed) at approximately 14q24, which are contained within partially overlapping clones, AL160191.3 and AL135747.4. Thus clearly one would not simply be able to identify the 6 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were. Additionally, it should be noted that the human Na+/Ca+ exchanger, SLC8A3 gene also maps to the same region of human chromosome 14 (14q24). This further supports Applicant's position that the

sequences of the present invention encodes a variant of the human Na+/Ca+ exchanger, SLC8A3.

Therefore, clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome.

The Action also discounts Applicants' assertion regarding the use of the presently claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic. Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences

would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human

genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). The sequences of the present invention have particularly specific utility in DNA gene chip based analysis as they have been identified to contain several coding region nucleotide polymorphisms (see above), thus increasing their utility in DNA gene chip based analysis.

Finally, the Examiner is requested to consider the issue of due process. Applicants understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter. As the issued U.S. Patents cited above are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph, Applicants

respectfully submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101.

Thus in summary, Applicants submit that the presently claimed molecules have been shown to encode, as asserted in the specification as filed, Na+/Ca+ exchanger isoforms, whose biological function is known to the art. Thus, the present situation directly tracks Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the 100 % identity between the presently claimed sequences and those of the cited Na+/Ca+ exchanger isoform (SLC8A3). Furthermore this response has described a series of additional substantial, specific, credible and well-established utilities for the present invention. Therefore, Applicants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of the claims under 35 U.S.C. § 101 has been overcome. Thus, Applicants respectfully request that the rejection be withdrawn.

V. Rejection of Claims 1-4 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Applicants respectfully submit that claims 1-4 have been shown to have "a specific, substantial, and credible utility", as detailed in the section IV above. Applicants therefore request that the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claim 2 under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 2 stands rejected because the phrase "stringent conditions" is alleged to be indefinite. Although Applicants believe that this claim as originally filed sufficiently points out and distinctly claims the

invention, in order to more rapidly progress the case to allowance, Applicants have amended claim 2 to specify "highly" stringent conditions. Highly stringent conditions for full-length molecules are defined in the specification on page 4, line 32-page 5, line 5. Applicants invite the Examiners attention to the fact that, in addition to the example given, highly stringent conditions are well know in the art and are described at length in Current Protocols in Molecular Biology (Green Publishing Associates, Inc., and John Wiley & Sons, Inc., NY) which is incorporated by reference into the specification of the present invention. Applicants, therefore, respectfully submit that this rejection has been avoided by Applicant's amendment of claim 2 to specify "highly" stringent conditions. Accordingly, the Examiner is respectfully requested to withdraw the pending rejection of claim 2 under 35 U.S.C. § 112, second paragraph.

VII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Nichols have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

July 22, 2003
Date

Peter G. Schuman
Reg. No. 40,162

Lance K. Ishimoto Reg. No. No. 41,866
Agent for Applicants

LEXICON GENETICS INCORPORATED
(281) 863-3333

Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 10/054,680

1. (presently amended) An isolated nucleic acid molecule comprising the nucleotide sequence of the ion exchanger of SEQ ID NO: 1.

2. (presently amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

a. encodes the amino acid sequence shown in SEQ ID NO: 2; and

b. hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

3. (original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4. (original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4.

5. (new) A recombinant expression vector comprising the nucleic acid molecule of claim 3.

6. (new) A recombinant expression vector comprising the nucleic acid molecule of claim 4.

7. (new) A host cell comprising the recombinant expression vector of claim 5.

8. (new) A host cell comprising the recombinant expression vector of claim 6.

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 FASTA searches a protein or DNA sequence data bank
 version 3.3t05 March 30, 2000
Please cite:
 W.R. Pearson & D.J. Lipman PNAS (1988) 85:2444-2448

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               70        80        90       100       110       120
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              130       140       150       160       170       180
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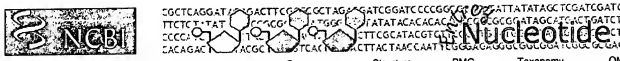

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3901 cccaattcca tatgtcccta ttatctcact cagctgacaa gacgtgaaaa tgagtcacat
3961 tcatgtggct ggggtggggt tctttttca ttgtaatcat tattgtggtt gctttcgttt
4021 tgccattagg ttttgcttat tattttgttt tgtctttttt ttctgaagtg agtgaaaaag
4081 gtgccacaaa ggaattccag gtccgagcca acagagagaa acatgaattt ttagacacat
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4741 ccctcaggtc acatatgaaa gcatttttac aagatagaga ctggaattcc tcatttctcc
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4921 gagatctccg tgccctacag acctttttctc aacgaatgtg ggaaggacct ggctttaaaa
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5041 ctttaggctt tctgcattga cataaataca ttttctaagg gggggggggg agaaattaaa
5101 aaacacctgt taatttttaaa cacatttttt aagaaaaaaa taattaaaaa agaaacagtg
5161 ctcatgtcat aagctatgtt gacagttgcc agtggaaatg ttgggttggt tcaaaaaaaa
5221 aataaaagct atactatatc tctctacata
//
```

EXHIBIT "D"

Gene. 2002 Sep 18;298(1):1-7.

The human SLC8A3 gene and the tissue-specific Na+/Ca2+ exchanger 3 isoforms.

Gabellini N, Bortoluzzi S, Danieli GA, Carafoli E.

Department of Biological Chemistry, University of Padova, Via G. Colombo, 3, 35121 Padua, Italy. nadia.gabellini@unipd.it

We have identified the human gene for member 3 of Solute Carrier family 8 (SLC8A3) by bioinformatic analysis of human genomic sequences. The gene is located on chromosome 14q24.2, and spans a region of about 150 kb. The full-length DNA complementary to RNA encoding the Na(+)/Ca(2+) exchanger isoform 3 (NCX3), amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) from the human neuroblastoma SH-SY5Y RNA, includes seven exons and encodes a protein of about 100 kDa. RT-PCR analysis was performed in different tissues to determine the exon composition in the region encoding the large intracellular loop of the protein. The region underwent modifications by alternative tissue-specific splicing. NCX3.2, including exon 4 but not exon 5, was found in human brain and in the neuroblastoma cell line. In human skeletal muscle two additional isoforms were identified: NCX3.3, including exons 4 and 5, and a truncated isoform (NCX3.4) produced by the skipping of both exons 3 and 4. The skipping causes a frame shift downstream of the exon 2 sequence. The new coding sequence of 25 amino acids terminates with a stop codon in exon 6. The NCX3.4 isoform (68 kDa) is truncated in the C-terminal portion of the domain first found in Drosophila Na(+)/Ca(2+) exchanger domain (Calxbeta) and lacks the C-terminal hydrophobic segments.

PMID: 12406570 [PubMed - indexed for MEDLINE]

Home **Paracel BLAST Results** Help

MEGABLAST 1.2.3-Paracel [2001-11-20]

Reference:
Zheng Zhang, Scott Schwartz, Lukas Wagner, and Webb Miller (2000),
"A greedy algorithm for aligning DNA sequences",
J Comput Biol 2000; 7(1-2):203-14.
Database: Homo_sapiens.latestgp.masked.fa
33,840 sequences; 200,810,911,373 total letters

Query= MEM260
(2766 letters)

Sequences producing significant alignments:	Score (bits)	E Value
AL160191.3.1.206256	3531	0.0
AL135747.4.1.173275	755	0.0
AC073548.5.1.167722	234	2e-58
AC007281.3.1.179343	155	2e-34
AC007377.3.1.144294	125	2e-25
AC007254.3.1.136417	98	4e-17

>AL160191.3.1.206256
Length = 206256

Score = 3531 bits (1781), Expect = 0.0
Identities = 1784/1785 (99%)
Strand = Plus / Plus

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Query: 1      atggcgtggttaaggttgcagcctctcacctctgccttcctccatttgggctggttacc 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 95395  atggcgtggttaaggttgcagcctctcacctctgccttcctccatttgggctggttacc 95454

Query: 61     tttgtgctcttcctgaatggtcttcgagcagaggctggtggctcaggggacgtgccaagc 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 95455  tttgtgctcttcctgaatggtcttcgagcagaggctggtggctcaggggacgtgccaagc 95514

Query: 121    acagggcagaacaatgagtcctgttcagggtcatcggactgcaaggagggtgtcatcctg 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 95515  acagggcagaacaatgagtcctgttcagggtcatcggactgcaaggagggtgtcatcctg 95574

Query: 181    ccaatctggtacccggagaaccctccctggggacaagattgccagggtcattgtctat 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 95575  ccaatctggtacccggagaaccctccctggggacaagattgccagggtcattgtctat 95634

Query: 241    tttgtggccctgatatacatgttccttggggtgtccatcattgctgaccgcttcatggca 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 95635  tttgtggccctgatatacatgttccttggggtgtccatcattgctgaccgcttcatggca 95694

Query: 301    tctattgaagtcatcacctctcaagagagggaggtgacaattaagaaacccaatggagaa 360
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Sbjct: 95695 tctattgaagtcatcacctctcaagagagggaggtgacaattaagaaacccaatggagaa 95754

Query: 361   accagcacaaccactattcgggtctggaatgaaactgtctccaacctgacccttatggcc 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 95755 accagcacaaccactattcgggtctggaatgaaactgtctccaacctgacccttatggcc 95814

Query: 421   ctgggttcctctgctcctgagatactcctctctttaattgaggtgtgtggtcatgggttc 480
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Query: 481   attgctggtgatctgggaccttctaccattgtagggagtgcagccttcaacatgttcatc 540
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Sbjct: 95875 attgctggtgatctgggaccttctaccattgtagggagtgcagccttcaacatgttcatc 95934

Query: 541   atcattggcatctgtgtctacgtgatcccagacggagagactcgcaagatcaagcatcta 600
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Query: 601   cgagtcttcttcatcaccgctgcttggagtatctttgcctacatctggctctatatgatt 660
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Query: 661   ctggcagtcttctcccctggtgtggtccaggtttggggaaggcctcctcactctcttcttc 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 96115 tttccagtgtgtgtccttctggcctgggtggcagataaacgactgctcttctacaaatac 96174

Query: 781   atgcacaaaaagtaccgcacagacaaacaccgaggaattatcatagagacagagggtgac 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 96175 atgcacaaaaagtaccgcacagacaaacaccgaggaattatcatagagacagagggtgac 96234

Query: 841   caccctaagggcattgagatggatgggaaaatgatgaattcccatttctagatgggaac 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 96235 caccctaagggcattgagatggatgggaaaatgatgaattcccatttctagatgggaac 96294

Query: 901   ctggtgcccctggaagggaaggaagtggatgagtcccgcagagagatgatccggattctc 960
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Sbjct: 96295 ctggtgcccctggaagggaaggaagtggatgagtcccgcagagagatgatccggattctc 96354

Query: 961   aaggatctgaagcaaaaacacccagagaaggacttagatcagctggtggagatggccaat 1020
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Sbjct: 96355 aaggatctgaagcaaaaacacccagagaaggacttagatcagctggtggagatggccaat 96414

Query: 1021  tactatgctctttcccaccaacagaagagccgcgccttctaccgtatccaagccactcgt 1080
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                 |||||||||||||||||||||||||||||||||| ||||||||||||||||||||||||||
Sbjct: 96415 tactatgctctttcccaccaacagaagagccgtgccttctaccgtatccaagccactcgt 96474

Query: 1081  atgatgactggtgcaggcaatatcctgaagaaacatgcagcagaacaagccaagaaggcc 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 96475 atgatgactggtgcaggcaatatcctgaagaaacatgcagcagaacaagccaagaaggcc 96534

Query: 1141  tccagcatgagcgaggtgcacaccgatgagcctgaggactttatttccaaggtcttcttt 1200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Query: 1201  gacccatgttcttaccagtgcctggagaactgtggggctgtactcctgacagtggtgagg 1260
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Query: 1441  tttgtaaggttgagcaatgtccgcatagaggaggagcagccagaggaggggatgcctcca 1500
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Query: 1561  gttaccatcttggatgatgaccatgcaggcatcttcacttttgaatgtgatactattcat 1620
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Query: 1621  gtcagtgagagtattggtgttatggaggtcaaggttctgcggacatcaggtgcccggggt 1680
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Query: 1681  acagtcatcgtccccttaggacagtagaagggacagccaagggtggcggtgaggacttt 1740
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Sbjct: 97075 acagtcatcgtccccttaggacagtagaagggacagccaagggtggcggtgaggacttt 97134

Query: 1741  gaagacacatatggggagttggaattcaagaatgatgaaactgtg 1785
```

```
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Sbjct: 97135 gaagacacatatggggagttggaattcaagaatgatgaaactgtg 97179


 Score =  210 bits (106), Expect = 4e-51
 Identities = 109/110 (99%)
 Strand = Plus / Plus


Query: 1785   gaaaaccataagggttaaaatagtagatgaggaggaatacgaaaggcaagagaatttctt 1844
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Query: 1845   cattgcccttggtgaaccgaaatggatggaacgtggaatatcagatgtga 1894
               ||||||||||||||||||||||||||||||||||||||||||| |||||
Sbjct: 202932 cattgcccttggtgaaccgaaatggatggaacgtggaatatcaggtgtga 202981


>AL135747.4.1.173275
          Length = 173275

 Score =  755 bits (381), Expect = 0.0
 Identities = 381/381 (100%)
 Strand = Plus / Plus


Query: 2386  ccagatacgtttgccagcaaagctgctgcccctccaggatgtatatgcagacgcctccatt 2445
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Query: 2446  ggcaacgtgacgggcagcaacgccgtcaatgtcttcctgggcatcggcctggcctggtcc 2505
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Query: 2506  gtggccgccatctactgggctctgcagggacaggagttccacgtgtcggccggcacactg 2565
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Query: 2566  gccttctccgtcaccctcttcaccatctttgcatttgtctgcatcagcgtgctcttgtac 2625
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Sbjct: 31644 gccttctccgtcaccctcttcaccatctttgcatttgtctgcatcagcgtgctcttgtac 31703


Query: 2626  cgaaggcggccgcacctgggaggggagcttggtggccccccgtggctgcaagctcgccaca 2685
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 31704 cgaaggcggccgcacctgggaggggagcttggtggccccccgtggctgcaagctcgccaca 31763


Query: 2686  acatggctctttgtgagcctgtggctcctctacatactctttgccacactagaggcctat 2745
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 31764 acatggctctttgtgagcctgtggctcctctacatactctttgccacactagaggcctat 31823


Query: 2746  tgctacatcaaggggttctaa 2766
```

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                |||||||||||||||||||||
Sbjct: 31824 tgctacatcaaggggttctaa 31844


 Score =  553 bits (279), Expect = e-154
 Identities = 279/279 (100%)
 Strand = Plus / Plus

Query: 2111  cagcaggggatgaggatgaggatgaatccggggaggagaggctgccctcctgctttgact 2170
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 28746 cagcaggggatgaggatgaggatgaatccggggaggagaggctgccctcctgctttgact 28805

Query: 2171  acgtcatgcacttcctgactgtcttctggaaggtgctgtttgcctgtgtgccccccacag 2230
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Query: 2231  agtactgccacggctgggcctgcttcgccgtctccatcctcatcattggcatgctcaccg 2290
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Query: 2291  ccatcattggggacctggcctcgcacttcggctgcaccattggtctcaaagattcagtca 2350
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Query: 2351  cagctgttgttttcgtggcatttggcacctctgtcccag 2389
              |||||||||||||||||||||||||||||||||||||||
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 Score =  254 bits (128), Expect = 3e-64
 Identities = 128/128 (100%)
 Strand = Plus / Plus

Query: 1886  cagatgtgacagacaggaagctgactatggaagaagaggaggccaagaggatagcagaga 1945
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Query: 1946  tgggaaagccagtattgggtgaacaccccaaactagaagtcatcattgaagagtcctatg 2005
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 25734 tgggaaagccagtattgggtgaacaccccaaactagaagtcatcattgaagagtcctatg 25793

Query: 2006  agttcaag 2013
              ||||||||
Sbjct: 25794 agttcaag 25801


 Score =  210 bits (106), Expect = 4e-51
 Identities = 109/110 (99%)
 Strand = Plus / Plus
```

```
Query: 1785  gaaaaccataagggttaaaatagtagatgaggaggaatacgaaaggcaagagaatttctt 1844
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Sbjct: 16852 gaaaaccataagggttaaaatagtagatgaggaggaatacgaaaggcaagagaatttctt 16911


Query: 1845  cattgcccttggtgaaccgaaatggatggaacgtggaatatcagatgtga 1894
             ||||||||||||||||||||||||||||||||||||||||||| |||||
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 Score =  202 bits (102), Expect = 9e-49
 Identities = 102/102 (100%)
 Strand = Plus / Plus


Query: 2012  agactacggtggacaaactgatcaagaagacaaacctggccttggttgtggggacccatt 2071
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 26682 agactacggtggacaaactgatcaagaagacaaacctggccttggttgtggggacccatt 26741


Query: 2072  cctggagggaccagttcatggaggccatcaccgtcagtgcag 2113
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>AC073548.5.1.167722
          Length = 167722

 Score =  234 bits (118), Expect = 2e-58
 Identities = 200/227 (88%), Gaps = 2/227 (0%)
 Strand = Plus / Minus


Query: 2141  gggaggagaggctgccctcctgctttgactacgtcatgcacttcctgactgtcttctgga 2200
             |||||||| ||||||| || ||||||||||||||| ||||||||||||| || |||||||
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Query: 2201  aggtgctgtttgcctgtgtgccccccacagagtactgccacggctgggcctgcttcgccg 2260
             |||||||| || |||||||||||||||| ||||||||||||||||||||||||| |  |
Sbjct: 77829 aggtgctcttcgcctgtgtgccccccaccgagtactgccacggctgggcctgctttggtg 77770


Query: 2261  tctccatcctcatcattggcatgctcaccgccatcattggggacctggcctcgcacttcg 2320
             |||||||||| |||| ||| |||||||||| |||||||||||| ||||| |||||||
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Query: 2321  gctgcaccattggtctcaaagattcagtcaca-gctgttgttttcgt 2366
             |||||||| |||| ||||| || || |||| | |||||||| ||||
Sbjct: 77709 gctgcaccgttggcctcaaggactctgtca-atgctgttgtcttcgt 77664


 Score = 58.0 bits (29), Expect = 3e-05
 Identities = 38/41 (92%)
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```
 Strand = Plus / Minus

Query: 1036   caccaacagaagagccgcgccttctaccgtatccaagccac 1076
              ||||| ||||||||||||||||||||||| ||||| |||||
Sbjct: 102711 caccagcagaagagccgcgccttctaccgcatccaggccac 102671


 Score = 52.0 bits (26), Expect = 0.002
 Identities = 137/173 (79%), Gaps = 6/173 (3%)
 Strand = Plus / Minus

Query: 523    gccttcaacatgttcatcatcattggcatctgtgtctacgtgatcccagacggagaga-c 581
              |||||||||||||| | |||| | | | ||  ||||||| ||||||| ||| |||| |
Sbjct: 111370 gccttcaacatgtttgtggtcatcgccgtgtgcatctacgtcatcccagccggcgagagc 111311

Query: 582    tcgcaagatcaagcatct-acgagtcttcttcatcaccgc-tgcttggagtatctttgcc 639
              |||||||||||||||| || | |||||||||||  |||| || | ||||||| ||||| |||
Sbjct: 111310 -cgcaagatcaagcacctga-gagtcttctttgtcactgcct-cttggagcatcttcgcc 111254

Query: 640    tacatctggctctatatgattctggcagtcttctcccctggtgtggtccaggt 692
              ||  ||||||| ||| | || || || || || ||||| ||||||||||||||
Sbjct: 111253 tatgtctggctttatctcatccttgctgtttttttccccccggtgtggtccaggt 111201


>AC007281.3.1.179343
          Length = 179343

 Score =  155 bits (78), Expect = 2e-34
 Identities = 420/532 (78%), Gaps = 12/532 (2%)
 Strand = Plus / Plus

Query: 200    acccttcccttggggacaagattgccag-ggtcattgtctattttgtggccctgatatac 258
              |||||||  |||||||||| ||||| || | | | ||| |||||||||||| || | |||
Sbjct: 15320 acccttcttttggggacaaaattgctagagct-actgtgtattttgtggccatggtctac 15378

Query: 259    atgttccttggggtgtccatcattgctgaccgcttcatggcatctattgaagtcatcacc 318
              ||||| ||||| || || ||||| ||||| || |||||| | ||||| ||||||||||
Sbjct: 15379 atgtttcttggagtctctatcatagctgatcggttcatgtcctctatagaagtcatcaca 15438

Query: 319    tctcaagagagggaggtgacaattaagaaacccaatggagaaaccagcaca-accactat 377
              |||||||| |  ||  | || || |||||||||||||||| |||| || |.|| ||| |
Sbjct: 15439 tctcaagaaaaagaaataaccataaagaaacccaatggagagaccacca-agacaactgt 15497

Query: 378    tcgggtctggaatgaaactgtctccaacctgaccctt-atggccctgggttcctctgctc 436
                || |||||||||||||| || || |||||||||| || |||||||||| || ||||||||
Sbjct: 15498 gaggatctggaatgaaacagtttctaacctgacc-ttgatggccctgggatcttctgctc 15556

Query: 437    ctgagatactcctctctttaattgaggtgtgtggtcatgggttcattgctggtgatctgg 496
              ||||||| ||||| ||  |||||||| |||||||| |||   |||| ||| || || || |
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```
Sbjct: 15557 ctgagattctcctttcagtaattgaagtgtgtggccataacttcactgcaggagacctcg 15616


Query: 497   gacctt-ctaccattgtaggga-gtgcagccttcaacatgttcatcatcattggca-tct 553
              | |||  | ||||| || |||| |||| || |||||| ||||||||||| |||| || |||
Sbjct: 15617 gtcctagc-accatcgt-gggaagtgctgcattcaatatgttcatcattattg-cactct 15673


Query: 554   gtgtctacgtgatcccagacggagagactcgcaagatcaagcatctacgagtcttcttca 613
              |||| || ||| | || |||||||||||  | ||||| |||||| | || ||||||||
Sbjct: 15674 gtgtttatgtggtgcctgacggagagacaaggaagattaagcatttgcgtgtcttctttg 15733


Query: 614   tcaccgctgcttggagtatctttgcctacatctggctctatatgattctggcagtcttct 673
              | || || || ||||| |||||||||||||| |||||| || || ||| || | ||| | |
Sbjct: 15734 tgacagcagcctggagcatctttgcctacacctggctttacattattttgtctgtcatat 15793


Query: 674   cccctggtgtggtccaggtttgggaaggcctcctcactctcttcttctttcctcc 725
              | |||||||| ||  |||| ||||||||  | || ||| ||||||||||||||
Sbjct: 15794 ctcctggtgttgtggaggtctgggaaggtttgcttactttctttcttctttcc 15845


>AC007377.3.1.144294
          Length = 144294

 Score =  125 bits (63), Expect = 2e-25
 Identities = 180/218 (82%), Gaps = 6/218 (2%)
 Strand = Plus / Plus


Query: 2131   gatgaatccggggaggagaggctgccctcctgcttt-gactacgtcatgcacttcctgac 2189
              |||||||  ||||| |||| |||||||||||||| ||| || ||||| |||||||| |||||
Sbjct: 126401 gatgaatgtggggaagagaagctgccctcctg-tttcgattacgtgatgcactttctgac 126459


Query: 2190   tgtcttctggaaggtgctgtttgcctgt-gtgccccccc-acagagtactgccacggctgg 2247
              ||| |||||||||||| |||||||||| | || |||||| || || |||||  | ||||||
Sbjct: 126460 tgtgttctggaaggtcctgtttgcct-tcgt-ccccccctactgaatactggaatggctgg 126517


Query: 2248   gcctgcttcgccgtctccatcctcatcattggcatgctcaccgccatcattggggacctg 2307
              || || |||   |||||||||||||||| |||||| | || || ||  |||||| ||||||
Sbjct: 126518 gcgtgtttcattgtctccatcctcatgattggcctactgacagctttcattggagacctg 126577


Query: 2308   gcctcgcacttcggctgcaccattggtctcaaagattc 2345
              || || ||||| ||||||||||||||| || ||||||||
Sbjct: 126578 gcttcccactttggctgcaccattggcctgaaagattc 126615


 Score = 50.1 bits (25), Expect = 0.008
 Identities = 31/33 (93%)
 Strand = Plus / Plus


Query: 2020   gtggacaaactgatcaagaagacaaaccctggcc 2052
              |||||||||||| || ||||||||||||||||||
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```
Sbjct: 105202 gtggacaaactcattaagaagacaaacctggcc 105234


>AC007254.3.1.136417
          Length = 136417

 Score = 97.6 bits (49), Expect = 4e-17
 Identities = 82/93 (88%)
 Strand = Plus / Plus


Query: 2428 tatgcagacgcctccattggcaacgtgacgggcagcaacgccgtcaatgtcttcctgggc 2487
            |||||||||||||||||| || ||||| |||||||||||||| || ||||||||||||||
Sbjct: 6375 tatgcagacgcctccataggtaacgtcacgggcagcaacgcggtgaatgtcttcctggga 6434


Query: 2488 atcggcctggcctggtccgtggccgccatctac 2520
            |||||  |||||||||||| | || |||||||||
Sbjct: 6435 atcggtgtggcctggtccatcgctgccatctac 6467



  Database: Homo_sapiens.latestgp.masked.fa
    Posted date:  May 12, 2003  5:02 PM
  Number of letters in database: 200,810,911,373
  Number of sequences in database:  33,840

Lambda     K      H
    1.37    0.711     1.31

Gapped
Lambda     K      H
    1.37    0.711     1.31


Matrix: blastn matrix:1 -3
Gap Penalties: Existence: 0, Extension: 0
Number of Hits to DB: 0
length of query: 5534
length of database: 200,810,911,373
effective HSP length: 22
effective length of query: 2744
effective search space used:         0
T: 0
A: 0
X1: 0 ( 0.0 bits)
X2: 20 (39.6 bits)
S1: 12 (24.3 bits)
S2: 24 (48.1 bits)
```